FURTHER WORK ON THE REDUCTION OF THE ALKALINITY OF THE BLOOD IN CHOLERA; AND SODIUM BICARBONATE INJECTIONS IN THE PREVENTION OF URAEMIA*

BY

SIR LEONARD ROGERS, KT., C.I.E., M.D., F.R.C.P.

PROFESSOR OF PATHOLOGY, MEDICAL COLLEGE, CALCUTTA

(*Received for publication* 21 *February*, 1916)

Early in 1915, in conjunction with Captain Shorten, I.M.S., I recorded estimations of the alkalinity of the blood in twenty cases of cholera, demonstrating its nearly constant reduction to well below the normal and showing that in cases of post-choleraic uraemia it reached the extreme degrees of from N/100 to N/240, thus confirming by accurate estimations the statement of Sellards (1910, 1914) that this dangerous condition is essentially an acidosis. On my collaboration with Captain Shorten being interrupted by the war, Dr. Satis Chandra Banerjee, to whom I am very greatly indebted for his careful observations, kindly undertook the estimations of the alkalinities of the blood in cholera cases in my ward. In a recent paper (1915) on the results of my system of treatment in 1,000 cases of cholera, I gave a table briefly summarising the results of the test in sixty-two cases. As the number has now risen to upwards of one hundred spread over a complete year, and consequently

* With a 'Note on the Technique of the Estimations of the Alkalinity of the Blood,' by Satis Chandra Banerjee, L.M.S. See page 150.

including all degrees of severity, I propose in the present paper to analyse the records more fully, and to record the results of the routine administration of alkalies intravenously from an early stage of the disease in combating the condition, and their effect in greatly reducing the mortality from the dreaded post-choleraic uraemia.

Table I shows the degree of reduction of the alkalinity of the blood before the administration of alkalies in 104 unselected cases of cholera, taken, in nearly all of them, on admission to hospital. The higher proportion with alkalinities above N/45 in this series, as compared with the series of 62 cases recorded in the paper already referred to, is due to the additional cases having mostly occurred in the rainy season, when the mildest type of cholera prevails in Calcutta.

Table I.—The Degrees of Reduction of the Alkalinity and the Causes of Death in 104 Cholera cases.

Alkalinity	Cured	Died			Total deaths	Total cases	Percentage of deaths	Percentage		
		Collapse	Uraemia	Other causes						
Over N/45	21	1	1	1	3	24	12·5	23·1		
N/45–N/60	21	3	—	—	3	24	12·5	23·1		
N/60–N/80	21	2	1	—	3	24	12·5	23·1		76·9
N/80–N/100	16	4	1	1	6	22	27·3	21·1	53·8	
N/100 and less	4	2	4	—	6	10	60·0	9·6	30·7	
Totals	83	12	7	2	21	104				

The data in Table I show that in 77 per cent. of cholera cases the alkalinity of the blood is reduced to N/45 and under, while in no less than 53·9 per cent. it was N/60 and under, while in 30·7 per cent. it reached the extreme degrees of from N/80 to N/240. Moreover, when the alkalinity fell to N/80 and under, the death rate rose markedly from 12·5 to 27·3 per cent., and in cases with alkalinities of 100 and under it reached the very high figure rate of 60 per cent. On turning to the causes of death, it appears that

when the alkalinity falls to N/80, and under, the proportion of deaths in the collapse stage greatly increases, indicating that there is a close relationship between the degree of reduction of the alkalinity and the severity of the disease, quite apart from the question of uraemic complication. Further, when the alkalinity falls to N/100, and below, the death rate from uraemia rises to an extremely high figure, namely, 40 per cent. of the cases, and would have been still higher but for the injections of alkalies as described below.

In cases admitted in the acute stage the specific gravity of the blood on arrival is the best test of the severity of the disease, as it indicates the amount of fluid which has been lost from the body; 1063, 1064, and 1065 pointing to an approximate loss of three, four, and five pints respectively in a subject not previously anaemic. Table II shows a progressively larger proportion of cases with the

Table II.—The Relationship of the Specific Gravity of the Blood on admission and the Alkalinity.

Alkalinity	Specific gravity below 1060			Specific gravity 1060-1063			Specific gravity 1064-1065			Specific gravity over 1065		
	Cured	Died	Total	Cured	Died	Total	Cured	Died	Total	Cured	Died	Total
Over N/45 ...	4	—	4	8	1	9	5	1	6	4	1	5
N/45–N/60 ...	4	1	5 — 16 80%	7	1	8 — 21 75%	2	1	3 — 16 69·6%	8	—	8 — 20 60·6%
N/60–N/80 ...	7	—	7	2	2	4	6	1	7	6	1	7
N/80–N/100 ...	—	—	—	3	2	5	3	1	4	10	2	12
N/100 and less	—	4	4 — 4 20%	—	2	2 — 7 25%	3	—	3 — 7 30·4%	1	—	1 — 13 39·4%
Total	15	5	20	20	8	28	19	4	23	29	4	33

dangerously low alkalinities of N/80, and less, with an increase of the specific gravity of the blood on admission. All the four cases showing very low alkalinities with specific gravities on admission below 1060 were admitted late with uraemia, which ultimately

proved fatal, so none of the mild cases coming in the acute early stages showed very low alkalinities. Of the fairly mild cases, with specific gravities between 1060 and 1063, 25 per cent. showed very low alkalinities, while those with specific gravities of 1064 to 1065 and over 1065, respectively, showed 30·4 and 39·4 per cent. of very low alkalinities. The close relationship between the amount of fluid lost from the body and the decrease of the alkalinity of the blood confirms the opinion expressed in my previous paper with Captain Shorten, that the reduction of the alkalinity of the blood is an important and essential feature of cholera, and one which requires to be adequately dealt with in any complete and trustworthy system of treating this deadly disease.

Table III shows the alkalinity of the blood in relation to the

Table III.—Duration of the Disease and the Alkalinity of the Blood.

Alkalinities	To 12 hours				12 to 24 hours				24 to 48 hours				Over 48 hours			
	Cured	Died	Total	Percentage	Cured	Died	Total	Percentage	Cured	Died	Total	Percentage	Cured	Died	Total	Percentage
Under N/45 ...	11	2	13	27·7	4	1	5	19·2	4	—	4	22·2	2	—	2	15·4
N/45–N/60	8	2	10	21·3	5	—	5	19·2	6	1	7	39·0	2	—	2	15·4
N/60–N/80	10	2	12	25·5	4	—	4	15·4	4	—	4	22·2	3	1	4	30·8
N/80–N/100 ...	5	6	11	23·4	7	—	7	26·9	2	—	2	11·1	2	—	2	15·4
N/100 and less ...	—	1	1	2·1	2	3	5	19·2	1	—	1	5·5	1	2	3	23·0
Total	34	13	47		22	4	26		17	1	18		10	3	13	

duration of the disease before admission. The most noteworthy point it brings out is the high mortality among patients showing very low alkalinities within twelve hours of the commencement of the disease, no less than seven out of twelve having died, five from

collapse, one from uraemia and one from pneumonia, showing a high initial severity. Cases admitted between twenty-four and forty-eight hours of the onset are nearly always mild, and they showed the least reduction of the alkalinity. Those coming more than forty-eight hours after the onset showed alkalinities of N/60 and under in 70 per cent., and the three fatal cases all died of uraemia, having been admitted with suppression of urine of one to two days' duration.

THE VALUE OF INTRAVENOUS INJECTIONS OF SODIUM BICARBONATE IN THE PREVENTION OF POST-CHOLERAIC URAEMIA

In 1891, Wall recommended for intravenous injection in cholera a solution containing 0·4 per cent. of sodium chloride and 0·2 per cent. of sodium bicarbonate, and many workers in India adopted his formula, although the amount of sodium chloride was dangerously low, for I found that such a solution haemolysed the blood in vitro. Sellards in 1910, in the Philippine Islands, observed that large amounts of alkalies could be tolerated by cholera patients with threatened uraemia without the urine being rendered alkaline, and he greatly reduced the death rate from post-choleraic uraemia by intravenous injections of sodium bicarbonate. Both Sellards in the Philippines, and J. W. D. Megaw, I.M.S., in Calcutta, however, found that once uraemic symptoms had supervened, it was too late, as a rule, to save the patient by alkaline injections. The earlier estimations of the alkalinity of the blood in my cholera cases by Captain Shorten, showing the constancy with which it is reduced and the extreme degree it reaches in post-choleraic uraemia, led me to inject solutions of sodium bicarbonate as a routine method in the early stages of cholera to prevent acidosis, in the following manner. All cases admitted on the first day of the disease, and requiring transfusion, received the hypertonic solution, namely, sodium chloride 120 grains and calcium chloride 4 grains in one pint. If the case were sufficiently severe to necessitate a second injection, the first pint consisted of sodium bicarbonate 160 grains (2 per cent.) and sodium chloride 60 grains, and this was followed by hypertonic solution up to the total amount required as

judged by the specific gravity of the blood, and this sequence was repeated with each subsequent transfusion. In cases admitted on the second or later day, if suppression of urine was present, the above alkaline solution was used at the first as well as at each subsequent injection. The bicarbonate of soda is sterilized in the solid form under pressure in weighed packets of 160 grains each and added to the sterile solution, so as to avoid the chemical changes which would result from boiling a solution of the alkaline salt.

Table V.—Amounts of Sodium Bicarbonate injected in relation to the Alkalinity of the Blood on admission.

Alkalinities	Nil			160 grains			320 grains			480-800 grains			960-1440 grains		
	Cured	Died	Total	Cured	Died	Total	Cured	Died	Total	Cured	Died	Total	Cured	Died	Total
Under N/45	9	—	9	5	1	6	1	1	2	2	—	2	—	—	—
N/45-N/60	13	1	14	7	1	8	1	1	2	—	—	—	1	—	1
N/60-N/80	4	—	4	9	—	9	1	1	2	6	—	6	—	3	3
N/80-N/100	4	—	4	4	5	9	3	1	4	1	—	1	2	1	3
N/100 and less ...	—	1	1	—	3	3	3	—	3	1	—	1	—	—	—
Total	30	2	32	25	10	35	9	4	13	10	—	10	3	4	7
Collapse	—	2	—	—	5	—	—	3	—	—	—	—	—	1	—
Uraemia	—	—	—	—	4	—	—	—	—	—	—	—	—	3	—
Others	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—

The first column of cases not receiving any alkalies includes all the mild cases requiring either no intravenous saline or only one hypertonic injection. The two cases which died of collapse were admitted with comparatively low specific gravities, probably due to previous anaemia. In the second column the cases received only

160 grains of sodium bicarbonate, namely, one pint of the 2 per cent. solution. No less than 4 out of the 35 died of uraemia, having been admitted 22, 22, 32 hours and 6 days respectively after the commencement of the disease, while in three of the four the specific gravity of the blood was below normal, so only subcutaneous injections could be given. They all occurred soon after I had commenced the alkaline injections, and before it was known what large quantities could safely be injected in post-choleraic uraemia, so it is possible that some of them might have been saved by early and repeated injections of sodium bicarbonate. The alkalinity on admission was found to be N/120 in two, and the extreme degree of N/240 in a third. The fourth case received five intravenous injections, but, unfortunately, sodium bicarbonate was only given once, this being one of the first cases in which it was used.

The third and fourth columns show a marked contrast to the above, for among twenty-three severe cases requiring several transfusions, but in whom from 320 to 800 grains of sodium bicarbonate were injected intravenously, not a single one was lost from uraemia; thus confirming the above opinion that too small amounts were injected in the fatal uraemia cases shown in the second column. The last column shows the worst cases in whom from four to seven intravenous injections were required, and three of them were eventually lost from uraemia in spite of the injections of from 960 to 1,440 grains of sodium bicarbonate intravenously in the course of several days. Two of the three were admitted fifty hours and four days respectively after the onset of the disease with prolonged suppression of urine, having come too late even for the alkaline injections to save them. The details of five cases are given in Table VI, which will serve to illustrate the principles of the treatment adopted for the prevention and control of post-choleraic uraemia. The daily figures of the specific gravity of the blood, blood pressure, alkalinity of the blood, saline injections, grains of sodium bicarbonate injected, and the ounces of urine passed daily, are given for each case.

In my book on cholera I gave a table on similar lines to the above, illustrating the relationship of the specific gravity of the blood and the blood pressure to the secretion of urine, and showing that a high specific gravity, indicating great concentration of the

TABLE VI.—Cases illustrating the use of Alkaline Injections in Cholera.

Duration on admission		Day in Hospital							Totals
		1	2	3	4	5	6	7	
Case 1—57 hours :—									
Specific gravity	1063	1051	1050	1054	1052	1050	—	—	—
Blood pressure	65mm.	105	115	120	115	107	—	—	—
Alkalinity	N/80	—	—	N/80	—	—	N/40	—	—
Pints of saline	—	5½	1	—	1	1	1	—	8½
Grains of sodium bicarbonate ...	—	320	160	160	—	160	160	—	960
Urine, ozs.	—	?	?	?	30	20	35	—	—
Case 2 :—									
Specific gravity	1064	1056	1063	1064	1060	1062	1058	—	—
Blood pressure	75mm.	93	94	90	101	104	101	—	—
Alkalinity	N/50	—	N/70	N/60	N/40	N/70	N/50	—	—
Pints of saline	—	4	3½	9	4	7	—	—	27½
Grains of sodium bicarbonate ...	—	160	160	320	160	320	—	—	1120
Urine, ozs.	—	22	28	28	38	16	43	—	—
Case 3—36 hours :—									
Specific gravity	1067	1062	1057	1061	1055	1061	1057	1057	—
Blood pressure	Nil	70	82	78	83	73	85	78	—
Alkalinity	N/80	—	—	—	N/40	—	N/40	—	—
Pints of saline	—	9	—	4	4	3	2	—	22
Grains of sodium bicarbonate ...	—	160	—	160	160	160	—	160	800
Urine, ozs.	—	?	6	20	58	18	16	52	—
Case 4—22 hours :—									
Specific gravity	1067	1057	1062	1063	1058	1055	1057	—	—
Blood pressure	Nil	82	90	97	93	112	116	—	—
Akalinity	—	—	N/80	N/52·5	N/65	N/80	N/80	—	—
Pints of saline	—	4	2	1	1	4	—	—	13
Grains of sodium bicarbonate ...	—	—	160	160	160	320	—	—	800
Urine, ozs.	—	6	14	9	0	20	50	—	—
Case 5—8 hours :—									
Specific gravity	1065	1063	1059	1064	1054	1056	1047	1054	—
Blood pressure	Nil	Nil	65	Nil	92	100	100	85	—
Alkalinity	—	—	—	N/80	—	N/80	—	N/100	—
Pints of saline	—	4½	9½	10	7	—	1	—	32
Grains of sodium bicarbonate ...	—	—	640	800	640	—	160	—	2240
Urine, ozs.	—	0	5	0	6	12	16	?	—

blood due to loss of fluid, and low blood pressure were the main factors in reducing the secretion of urine leading to post-choleraic uraemia. These points are also brought out in Table VI, and in addition the number of pints of saline and the amount of sodium bicarbonate in grains given daily are shown, together with the estimations of the alkalinity of the blood. The first four cases ended in recovery, and the last proved fatal. Where a ? is entered in the line showing the amount of urine passed daily, it means that the amount was very small and was passed either in the bed clothes or with the stool, so could not be measured. The following are the most important points brought out by these illustrative cases:—

Case 1 was admitted fifty-seven hours after the commencement of the disease with suppression of urine for thirty-eight hours, while the alkalinity on admission was found to have been reduced to the dangerously low point of N/80. In the first intravenous injection on admission 320 grains of sodium bicarbonate were therefore given, and in the course of the next five days four more doses of 160 grains each were injected subcutaneously, making a total of 960 grains. On the third day in hospital the alkalinity was still N/80, but on the sixth day it rose to N/40. During the first three days only very small quantities of urine were passed, but from the fourth day it began to be passed in fair quantities, and he made a good recovery.

Case 2 was also a very severe one, requiring no less than seven intravenous salines amounting to a total of $27\frac{1}{2}$ pints, in which 1,120 grains of sodium bicarbonate were given. The alkalinity was thus prevented from falling below N/70, and the patient recovered.

Case 3 was admitted with the very high specific gravity of 1067, and with no pulse at the wrist. The alkalinity was N/80, and he received 22 pints of saline, containing 800 grains of sodium bicarbonate, intravenously in the course of six days. During the first two days very little urine was passed, but on the fourth day the alkalinity had risen to N/40, and 58 ounces of urine were passed, and she made a good recovery.

Case 4 was also a very severe one, admitted with a specific gravity of 1067, and pulseless. On the second day the alkalinity was found to be reduced to N/80, and the urine was scanty, so

injections of sodium bicarbonate were begun. On the third and fourth days there was complete suppression of urine, but after 800 grains of sodium bicarbonate had been injected intravenously, in the course of four days the secretion of urine became re-established, and the patient made a good recovery from a most dangerous condition.

Case 5 was a most remarkable one, requiring no less than ten intravenous injections, containing 2,240 grains of sodium bicarbonate, in the course of six days. Yet the alkalinity could not be raised above N/80, while it fell to N/100 on the seventh day, and the urinary secretion, which had recommenced on the fifth day, after almost complete suppression for four days, again declined, the blood pressure fell, and the patient died of exhaustion, his life having undoubtedly been greatly prolonged by the alkaline injections, although his strength gave out in the end.

The above cases will suffice to illustrate the great value of the sodium bicarbonate injections in preventing the alkalinity falling to the very low point of N/100 or less, which nearly always ends in fatal uraemia. This method of dealing with the decreased alkalinity of the blood, which has now been shown to be such a constant and important feature of severe cholera, has been used throughout 1915, and the result on the death rate from uraemia is shown in Table VII.

Table VII.—Yearly death rates from Uraemia.

Year	Total cases	Uraemia deaths	Percentage		
1912	170	24	14·1		
1913	200	17	8·5	11·1	Without alkalies
1914	222	25	11·2		
1915	225	6	2·7	2·7	With alkalies

It will be seen from Table VII that the addition of alkalies intravenously in 1915 has led to a reduction of the death rate from

uraemia from an average of 11·1 among 592 cases from 1912 to 1914, to one of only 2·7 among 225 cases in 1915, or a decrease of 75·7 per cent. in the mortality from this cause. Moreover, of the six patients lost from uraemia during 1915, three were admitted two or more days after the onset of the attack of cholera with prolonged suppression of urine, so were brought too late for even the alkaline injections to save them.

CONCLUSION

The extensive series of estimations of the alkalinity of the blood in cholera cases dealt with in this paper allows me to go much further than in my first paper with Captain Shorten, in which I came to the conclusion that it was advisable to give intravenous injections of alkalies in cases showing deficient urinary secretion without waiting for uraemic symptoms to develop. Now that my observations have shown that the alkalinity of the blood is nearly always very much reduced in severe cases of cholera, and that the early and repeated administration of sodium bicarbonate intravenously has lowered the mortality from uraemia to one-fourth of its former rate, it is now clear that the rule I have adopted of giving alkalies intravenously in all cases of cholera with each saline injection after the first, as well as with the first injection in late admissions with deficient urinary secretion, is a sound one which should never be neglected.

NOTE ON THE TECHNIQUE OF THE ESTIMATIONS OF THE ALKALINITY OF THE BLOOD

BY

SATIS CHANDRA BANERJEE, L.M.S.

The alkalinity of a solution of chemical substance depends on the presence of free OH ions, and it can actually be measured by methods of Physical Chemistry. But the alkalinity of blood, containing organic and inorganic substances, as well as blood corpuscles which have a different composition from the plasma in which they float, cannot be ascertained by simply measuring the presence of free OH ions.

If alkalinity be measured by the free OH ions, then blood is practically a neutral fluid. But if we take the power of combining with acid as a measure for alkalinity, the blood is distinctly alkaline.

Blood has the power of combining with both acid and alkali, owing to the presence of acid phosphates in combination with proteins as well as inorganic salts Na_2HPO_4, $NaHCO_3$, NaH_2PO_4, etc., and the measure of such power is dependent on the indicator used; for example, blood serum is acid to phenolphthalin, but it is alkaline to litmus. As its acid-combining power is greater than that for alkali, titrimetrically it must be called an alkaline fluid.

Although the titration method does not give us the true neutral point, and, therefore, the degree of alkalinity or acidity, yet it gives a measure of the amount of acid or alkali which can be added to the fluid without raising the OH ion concentration or H ion concentration above certain low limiting values (Rogers and Shorten).

The peculiar content of blood, in proteins, in carbonates and phosphates of alkali metals, increases the possibility of the amount of acid or alkali which can be set free in the body without causing OH or H ionic concentration to rise so high as to disturb or prevent the metabolic processes in the protoplasm, which are necessary for life (Moore and Wilson).

Again when the serum alone is used for estimation, the alkaline principles of the clot are excluded, and if laked blood is used some uncertain chemical processes are taken into account.

Healthy blood serum contains fairly constant alkaline substances whose alkalinity or power of combining with acid can be easily ascertained by the method described below. From variation in this acid-combining power of blood, we can have an idea of the presence of profound changes in its chemical constitution as is found in cholera, diabetic kala-azar coma, etc., and prompt measures can be taken to bring the alkalinity to, or near, the normal level.

METHOD

The alkalinity of blood was determined by Wright's method, slightly modified. Capsules in which blood is collected are prepared according to directions given by Dr. Wright in his book 'Technique of Teat and Capillary Tube.' The curved end of the capsule should be brought so close as to admit the whole into the bucket of the centrifugal machine. The capsules and pipettes are all carefully neutralised (as in the process of preparation they become alkaline) by washing with weak sulphuric acid, then with tap water, and lastly with distilled water. The two ends of the capsule are broken and to one end a rubber tube is attached, and the washing fluid is sucked in and out several times until the washings with distilled water are neutral (as tested with litmus paper).

After washing, the capsules are completely dried by blowing air through them. Special care should be taken so that no drop of water remains inside.

A capillary pipette with a rubber tube, or Wright's throttle pipette with a rubber teat, can be used. A mark is made on the pipette with paraffin pencil, about 1 or 2 cm. from its end, to mark the unit volume of serum or acid solution.

Blood is collected from the tip of a finger, which should be cleaned beforehand with ether, and a certain time allowed for its complete evaporation. A large puncture is made, and the capsule filled with blood in the usual way, and the ends of the capsule are

sealed by pushing them through melted sealing wax. These should never be sealed by heating.

The capsules are kept in the vertical position, and sufficient time allowed for the serum to separate by centrifugalisation, so that it may be obtained quite free from red corpuscles.

Stock solutions of sulphuric acid of the following strengths are prepared, viz.:—N/25, N/30, N/35, N/40, N/45, N/50, N/55, N/60, N/65, N/70, N/80. If further dilutions are required, they can be prepared at the time of working, small quantities of different solutions being placed in separate glass cups or staining blocks (provided with covers so that the strengths of the solutions are not altered by evaporation).

Place in position a clean slide and a few sensitised red litmus papers (prepared according to the direction of Dr Wright).

Break the capsule containing blood by making a nick with a file a little higher than the level of the blood. Insert the end of pipette and suck or draw in unit volume of serum, then draw in a bubble of air, and again draw in unit volume of any acid solution with which it is to be titrated. Eject both of these on the glass slide. Then mix them by drawing up and ejecting four or five times—then again draw a small part of this mixture and eject it on to the surface of the litmus paper. If a blue colour is not produced, repeat the process with a weaker solution until one is found which gives just a faint blue colour. The alkalinity is between this and the one above it, giving no blue colour, and so is the mean of the two.

REFERENCES

Moore, B., and Wilson, F. P. (1906). A clinical method of Haemalkalimetry, etc. *Bio-Chemical Journ.*, I, pp. 297-327.

Rogers, L. (1915). The results of the hypertonic and Permanganate treatment in 1,000 cases of Cholera; with remarks on the value of alkalies in the prevention of Uraemia and the rôle of atropine. *Lancet*, July 31, pp. 219-223.

Rogers, L., and Shorten, A. J. (1915). The alkalinity of the blood in kala-azar and cholera, and the technique of its estimation. *Ind. Journ. Med. Research*, II, pp. 867-881.

Sellards, A. W. (1914). Renal lesions of Cholera and Acidosis. *Amer. Journ. Trop. Dis. and Prev. Med.*, II, pp. 104-117.